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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/583,369	05/24/2007	Peter R. Brink	13533/48203	3149

26646 7590 09/16/2008  
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NEW YORK, NY 10004

EXAMINER
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GIBBS, TERRA C

ART UNIT	PAPER NUMBER
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1635

MAIL DATE	DELIVERY MODE
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09/16/2008

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b>		<b>Applicant(s)</b>	
	10/583,369		BRINK ET AL.	
	<b>Examiner</b>		<b>Art Unit</b>	
	TERRA C. GIBBS		1635	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 08 September 2008.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-23 is/are pending in the application.
- 4a) Of the above claim(s) 15-18 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-14 and 19-23 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 19 June 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |                                                                                        |                                                                   |
|----------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____.                                     |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>6/19/2006 and 9/20/2007</u> .                                 | 6) <input type="checkbox"/> Other: _____.                         |

### **DETAILED ACTION**

This Office Action is a response to Applicant's Election filed September 8, 2008.

Claims 1-23 are pending in the instant application.

### ***Election/Restrictions***

Applicant's election with traverses of Group I, claims 1-14, drawn to a method of delivering an oligonucleotide or a plasmid expressing an oligonucleotide into a target cell comprising introducing the oligonucleotide into a target cell and contacting the target cell with the donor cell under conditions permitting the donor cell to form a gap junction channel, wherein the gap junction channel is composed of connexin 43, in the reply filed on September 8, 2008 is acknowledged. The traversal is on the ground(s) that it would not be an undue burden for the Examiner to conduct a search for the five different connexins specified in Groups I-V.

This argument has been considered but is not found persuasive because, contrary to Applicant's argument, it would be an undue burden for the Examiner to conduct a search for the five different connexins specified in Groups I-V. For example, and as discussed in the previous Restriction Requirement mailed July 7, 2008, the inventions of Groups I-V are patentably distinct from each other since they are directed to methods of delivering an oligonucleotide or a plasmid expressing an oligonucleotide into a target cell under conditions permitting the formation of uniquely different gap junction channels, namely gap junction channels expressing connexin 43, connexin 40, connexin 45, connexin 32, and connexin 37, respectively. The uniquely different gap

junction channels formed by Groups I-V are known in the art to possess materially different design (e.g. nucleic acid sequence). Therefore, the prior art applicable to one invention would not likely be applicable to another invention and the claimed connexin genes containing different nucleic acid sequences are likely to raise different non-prior art issues. Because Groups I-V are known in the art to possess materially different designs, the claimed inventions require a different field of search because they employ different search queries as it relates to their individual nucleic acid sequence content. Since it is an undue burden to search and examine these multiple inventions in a single application, due to the fact that the searches are divergent and non-coextensive, and require different search queries for examination purposes, restriction is proper therefore.

In this regard, claims 15-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction requirement in the reply filed on September 8, 2008.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 1-14 and 19-23 have been examined on the merits.

### ***Priority***

Applicant's reference to priority in the first sentence of the specification is acknowledged.

***Information Disclosure Statement***

Applicant's information disclosure statements filed June 19, 2006 and September 20, 2007 are acknowledged. The submissions are in compliance with the provisions of 37 CFR §1.97. Accordingly, the Examiner has considered the information disclosure statements and signed copies are enclosed herewith.

***Specification***

It is noted that the instant specification at page 9 lists several non-patent literature. If Applicants wish to have these references considered by the Office, Applicants should include them in an information disclosure statement filed under 37 CFR § 1.97.

***Drawings***

The drawings filed on June 19, 2006 are acknowledged and have been accepted by the Examiner.

***Claim Objections***

Claim 19 is objected to because of the following informalities: In claim 19, line 2, the word "connexion" is improperly spelled and should be correctly spelled as "connexin". Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

Art Unit: 1635

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 and 19-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vitro* method of delivering an oligonucleotide or a plasmid expressing an oligonucleotide into a target cell comprising introducing the oligonucleotide into a target cell and contacting the target cell with the donor cell under conditions permitting the donor cell to form a gap junction channel, wherein the gap junction channel is composed of connexin 43, does not reasonably provide enablement for an *in vivo* method of delivering an oligonucleotide or a plasmid expressing an oligonucleotide into a target cell comprising introducing the oligonucleotide into a target cell and contacting the target cell with the donor cell under conditions permitting the donor cell to form a gap junction channel, wherein the gap junction channel is composed of connexin 43. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This is a scope enablement rejection.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

“Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*.

Art Unit: 1635

They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

The nature of the invention and the breadth of the claims:

The claims are drawn to a method of delivering an oligonucleotide or a plasmid expressing an oligonucleotide into a target cell comprising introducing the oligonucleotide into a target cell and contacting the target cell with the donor cell under conditions permitting the donor cell to form a gap junction channel, wherein the gap junction channel is composed of connexin 43. The broadness of the methods recited in the claims implies *in vivo* applicability for enablement purposes. The nature of the claimed invention, therefore, requires the knowledge of delivering oligonucleotides to cells in a human subject.

The amount of direction or guidance and presence/absence of working examples:

The specification teaches delivery of antisense oligonucleotides targeted to connexin 43 to cells in culture (see Figures, particularly Figures 1A-1D).

Applicant is reminded that during patent examination, the claims are given the broadest reasonable interpretation consistent with the specification. See MPEP § 2111-2116.01. The specification discloses that an oligonucleotide is introduced into a cell, wherein the cell is a human mesenchymal stem cell (see claim 9, for example). Thus, interpreted broadly, the claims encompass delivering an oligonucleotide to a target cell in a human subject. The specification as filed does not provide sufficient guidance or appropriate examples that would enable a skilled artisan to deliver an oligonucleotide to

a target cell in a human. Thus, although the specification considers and encompasses general methodologies of delivering oligonucleotides *in vivo*, such a disclosure would not be considered enabling since the state of nucleic acid-mediated gene delivery is highly unpredictable.

The state of the prior art and the predictability or unpredictability of the art:

The following references are cited herein to illustrate the state of the art of antisense delivery.

A review article by Braasch et al. (Biochemistry, 2002 Vol. 41, pages 4503-4510) specifically identify 3 factors that contribute to the unpredictable efficacy of using antisense compounds in general: 1) the variable capability of antisense oligonucleotides to access sites within the mRNA to be targeted; 2) problems pertaining to the delivery and uptake of the antisense oligonucleotides by cells, with the result that "the difference in oligonucleotide dose required to inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death"; and 3), that "oligonucleotides can bind to proteins and produce artifactual phenotypes that obscure effects due to the intended antisense mechanism".

The uptake of oligonucleotides by cells has been addressed by Agrawal et al. (Molecular Medicine Today, 2000 Vol. 6:72-81) who states that "[o]ligonucleotides must be taken up by cells in order to be effective....several reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is complex process; it depends on many factors, including



the cell type, the stage of the cell cycle, the concentration of serum. It is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency" (Page 378). "[M]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (Page 379).

Gewirtz et al. (Proc. Natl. Acad. Sci., 1996 Vol. 93:3161-3163) adds that, "[T]he other major problem in this field is the ability to deliver ODN (oligodeoxynucleotides) into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient."

Thus, it is maintained that the prior art at the time of Applicants' filing would not enable an *in vivo* method of delivering an oligonucleotide or a plasmid expressing an oligonucleotide into a target cell comprising introducing the oligonucleotide into a target cell and contacting the target cell with the donor cell under conditions permitting the donor cell to form a gap junction channel, wherein the gap junction channel is composed of connexin 43. Accordingly, one skilled in the art, being unable to use the prior art for such guidance, must necessarily find such guidance from the specification. However, one of skill would not find the guidance provided in the specification in the form of delivery of antisense oligonucleotides targeted to connexin 43 to cells in culture (*in vitro*) enough to overcome the unpredictability and challenges of delivering antisense *in vivo*, as exemplified in the references above. Thus, the specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with appropriate *in vivo* delivery of the antisense administered, and

specifically regarding the methods claimed.

In order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of how to deliver (*in vivo*) an oligonucleotide or a plasmid expressing an oligonucleotide into a target cell comprising introducing the oligonucleotide into a target cell and contacting the target cell with the donor cell under conditions permitting the donor cell to form a gap junction channel, wherein the gap junction channel is composed of connexin 43. Since the specification fails to provide any real guidance for delivering oligonucleotides *in vivo*, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In the absence of any real guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

### ***Claim Rejections - 35 USC § 102***

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 4, 8-12, 14, 20, 21, and 23 are rejected under 35 USC 102(a) as being anticipated by Frendo et al. (Journal of Cell Science, 2003 Vol. 116:3413-3421, submitted and made of record on Applicant's Information Disclosure Statement filed June 19, 2006).

Claims 1, 20, 21, and 23 are drawn to a method of delivering an oligonucleotide

into a target cell comprising introducing the oligonucleotide into a target cell and contacting the target cell with the donor cell under conditions permitting the donor cell to form a gap junction channel with the target cell, whereby the oligonucleotide is delivered into the target cell from the donor cell. Claims 3, 4, 8-12, and 14 depend from claim 1 and include all the limitations of claim 1 with the further limitations wherein the oligonucleotide is DNA; wherein the oligonucleotide is an antisense; wherein the oligonucleotide comprises 12-24 nucleotides; wherein the donor cell is a human mesenchymal stem cell; wherein the donor cell is a cell containing a connexin protein; wherein the target cell is present is a syncytial tissue selected from a cardiac myocyte, a smooth muscle cell, an epithelial cell; a connective tissue cell; and a syncytial cancer cell; and wherein the gap junction channel is composed of connexin 43. The broadness of the methods recited in the claims implies *in vitro* applicability for prior art purposes.

Frendo et al. disclose a method of delivering an antisense oligonucleotide targeted to connexin 43 to human trophoblast cells (see Abstract, for example). It is noted that human trophoblast cells express endogenous levels of connexin 43 and the antisense oligonucleotide targeted to connexin 43 was a 16-mer DNA oligonucleotide (see Abstract and Table 1, respectively). Upon antisense delivery, gap junctional intercellular communication was measured by fluorescence recovery after photobleaching (see Figure 4). While it is noted that connexin 43 antisense delivery greatly reduced cell-cell communication (e.g. the formation of gap junctions) in trophoblast cells, the presence of antisense did not completely abolish the percentage of coupled cells.

Therefore, claims 1, 3, 4, 8-12, 14, 20, 21, and 23 are anticipated by Frendo et al.

\*\*\*\*\*

Claims 1, 3, 4, 6, 10-12, 14, 20, 21, and 23 are rejected under 35 USC 102(b) as being anticipated by Li et al. (Journal of Cell Biology, 1996 Vol. 134:1019-1030).

The claims are as described above. Claim 6 is dependent on claim 1 and includes all the limitations of claim 1 with the further limitation wherein the oligonucleotide is a DNA that produces a peptide that can traverse the gap junction. The broadness of the methods recited in the claims implies *in vitro* applicability for prior art purposes.

Li et al. disclose a method of delivering an antisense oligonucleotide targeted to connexin 43 to Novikoff cells (see Abstract, for example). It is noted that Novikoff express endogenous levels of connexin 43 and the antisense oligonucleotide targeted to connexin 43 was a connexin 43 cDNA expressed from a plasmid in antisense orientation (see page 1025, second column and page 1021, second column, respectively). Upon antisense delivery, gap junction permeability and hemichannel activity was observed (see Table 1 and Figure 5, for example). While it is noted that connexin 43 antisense delivery greatly reduced gap junction communication in Novikoff cells, the presence of antisense did not completely abolish the percentage of coupled cells.

Regarding claim 6, Li et al. also disclose that HeLa cells do not endogenously express connexin protein(s), and therefore, HeLa cells were engineered to expression

connexin 43 (see page 1026, second column). In brief, the entire coding sequence of connexin 43 was expressed from a plasmid and transfected in HeLa cells and hemichannel activity was observed (see Figure 6, for example). It should be noted that the plasmid expressing the entire coding sequence of connexin 43 generates a protein/peptide that can traverse the gap junction.

Therefore, claims 1, 3, 4, 6, 10-12, 14, 20, 21, and 23 are anticipated by Li et al.

\*\*\*\*\*

Claims 1, 3, 4, 10-12, 14, 19, 20, 21, and 23 are rejected under 35 USC 102(b) as being anticipated by Burt et al. (American Journal of Physiology: Cell Physiology, 2001 Vol. 280:C500-C508).

The claims are as described above. Claim 19 is dependent on claim 1 and includes all the limitations of claim 1 with the further limitation wherein the gap junction channel is composed of at least two of connexin 43, connexin 40, connexin 45, connexin 32, and connexin 37. The broadness of the methods recited in the claims implies *in vitro* applicability for prior art purposes.

Burt et al. disclose a method of delivering an antisense oligonucleotide targeted to connexin 43 to A7r5 cells (see Abstract, for example). It is noted that A7r5 express endogenous levels of connexin 43 and connexin 40 (see Abstract, Figure 1 and Table 1). It is also noted that the antisense oligonucleotide targeted to connexin 43 was a connexin 43 cDNA expressed from a plasmid in antisense orientation (see page C510, first column). Upon antisense delivery, electrical coupling and dye coupling (e.g.

intercellular communication and gap junction permeability) was observed (see Table 3 and Figure 8, for example). While it is noted that connexin 43 antisense delivery greatly reduced gap junction communication in A7r5 cells, the presence of antisense did not completely abolish the percentage of cell coupling.

Therefore, claims 1, 3, 4, 10-12, 14, 19, 20, 21, and 23 are anticipated by Burt et al.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-14 and 19-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Frendo et al. (Journal of Cell Science, 2003 Vol. 116:3413-3421, submitted and made of record on Applicant's Information Disclosure Statement

filed June 19, 2006), Li et al. (Journal of Cell Biology, 1996 Vol. 134:1019-1030), or Burt et al. (American Journal of Physiology: Cell Physiology, 2001 Vol. 280:C500-C508) in view of Hammond et al. (Nature Reviews, 2001 Vol. 2:110-119).

Claims 1-3 and 20-23 are drawn to a method of delivering an oligonucleotide into a target cell comprising introducing the oligonucleotide into a target cell and contacting the target cell with the donor cell under conditions permitting the donor cell to form a gap junction channel with the target cell, whereby the oligonucleotide is delivered into the target cell from the donor cell, wherein the oligonucleotide is DNA or RNA. Claims 4-14 depend from claim 1 and include all the limitations of claim 1 with the further limitations wherein the oligonucleotide is an antisense; wherein the oligonucleotide is an siRNA; wherein the oligonucleotide comprises 12-24 nucleotides; wherein the oligonucleotide is a DNA or RNA that produces a peptide that can traverse the gap junction; wherein the donor cell is a human mesenchymal stem cell; wherein the donor cell is a cell containing a connexin protein; wherein the target cell is present is a syncytial tissue selected from a cardiac myocyte, a smooth muscle cell, an epithelial cell; a connective tissue cell; and a syncytial cancer cell; and wherein the gap junction channel is composed of connexin 43. The broadness of the methods recited in the claims implies *in vitro* applicability for prior art purposes.

*Determining the scope and contents of the prior art*

Frendo et al. teach a method of delivering an antisense oligonucleotide targeted to connexin 43 to human trophoblast cells (see Abstract, for example). It is noted that human trophoblast cells express endogenous levels of connexin 43 and the antisense

oligonucleotide targeted to connexin 43 was a 16-mer DNA oligonucleotide (see Abstract and Table 1, respectively). Upon antisense delivery, gap junctional intercellular communication was measured by fluorescence recovery after photobleaching (see Figure 4). While it is noted that connexin 43 antisense delivery greatly reduced cell-cell communication (e.g. the formation of gap junctions) in trophoblast cells, the presence of antisense did not completely abolish the percentage of coupled cells.

Li et al. teach a method of delivering an antisense oligonucleotide targeted to connexin 43 to Novikoff cells (see Abstract, for example). It is noted that Novikoff express endogenous levels of connexin 43 and the antisense oligonucleotide targeted to connexin 43 was a connexin 43 cDNA expressed from a plasmid in antisense orientation (see page 1025, second column and page 1021, second column, respectively). Upon antisense delivery, gap junction permeability and hemichannel activity was observed (see Table 1 and Figure 5, for example). While it is noted that connexin 43 antisense delivery greatly reduced gap junction communication in Novikoff cells, the presence of antisense did not completely abolish the percentage of coupled cells.

Regarding claim 6, Li et al. also teach that HeLa cells do not endogenously express connexin protein(s), and therefore, HeLa cells were engineered to expression connexin 43 (see page 1026, second column). In brief, the entire coding sequence of connexin 43 was expressed from a plasmid and transfected in HeLa cells and hemichannel activity was observed (see Figure 6, for example). It should be noted that



the plasmid expressing the entire coding sequence of connexin 43 generates a protein/peptide that can traverse the gap junction.

Burt et al. teach a method of delivering an antisense oligonucleotide targeted to connexin 43 to A7r5 cells (see Abstract, for example). It is noted that A7r5 express endogenous levels of connexin 43 and connexin 40 (see Abstract, Figure 1 and Table 1). It is also noted that the antisense oligonucleotide targeted to connexin 43 was a connexin 43 cDNA expressed from a plasmid in antisense orientation (see page C510, first column). Upon antisense delivery, electrical coupling and dye coupling (e.g. intercellular communication and gap junction permeability) was observed (see Table 3 and Figure 8, for example). While it is noted that connexin 43 antisense delivery greatly reduced gap junction communication in A7r5 cells, the presence of antisense did not completely abolish the percentage of cell coupling.

*Ascertaining the differences between the prior art and the claims at issue*

Neither Frendo et al., Li et al. nor Burt et al. teach that the oligonucleotide is an RNA or particularly an siRNA.

Hammond et al. teach that antisense and RNA interference are two methods of silencing expression of a gene and that RNA interference possesses characteristics that make it superior to antisense. For example, on page 110, first column, Hammond teaches that antisense methods are straightforward but suffer from “questionable specificity and incomplete efficacy”. RNA interference on the other hand, “has been shown in diverse organisms to inhibit gene expression in a sequence-specific manner” (same page and column) and requires only a few molecules of dsRNA per cell to

silence expression. Hammond also teaches that the RNA interference phenomenon in animals was discovered by researchers who were using antisense techniques and found that the use of double stranded instead of single-stranded RNAs reduced gene expression tenfold more efficiently (see paragraph bridging pages 110-111).

*Resolving the level of ordinary skill in the pertinent art*

The level of ordinary skill in the pertinent art is considered to be high, being a graduate student or post-doctoral fellow in a biological science.

*Considering objective evidence present in the application indicating obviousness or nonobviousness*

It would have been *prima facie* obvious to one of ordinary skill in the art, at the time the invention was made, to devise a method of delivering an oligonucleotide into a target cell comprising introducing the oligonucleotide into a target cell and contacting the target cell with the donor cell under conditions permitting the donor cell to form a gap junction channel with the target cell, whereby the oligonucleotide is delivered into the target cell from the donor cell, wherein the oligonucleotide is DNA using the teachings of either Frendo et al., Li et al. or Burt et al. It would have been *prima facie* obvious to one of ordinary skill in the art, at the time the invention was made to have the oligonucleotide consist of RNA using the teachings and motivation of Hammond et al.

One of ordinary skill in the art would have been motivated to devise a method of delivering an oligonucleotide into a target cell comprising introducing the oligonucleotide into a target cell and contacting the target cell with the donor cell under conditions permitting the donor cell to form a gap junction channel with the target cell, whereby the oligonucleotide is delivered into the target cell from the donor cell, wherein the

oligonucleotide is DNA since either Frendo et al., Li et al. or Burt et al. teach that such a method can determine the involvement of connexin in cell-to-cell communication. One of ordinary skill in the art would have been motivated to substitute the antisense oligonucleotide composed of DNA taught by either Frendo et al., Li et al. or Burt et al. with a RNA oligonucleotide because it is obvious to substitute one functional equivalent for another, particularly when they are to be used for the same purpose. See MPEP 2144.06. Further, one of ordinary skill in the art would have been motivated to substitute the antisense oligonucleotide composed of DNA taught by either Frendo et al., Li et al. or Burt et al. with a siRNA because Hammond et al. taught that siRNA are more preferred over traditional antisense technology.

One of ordinary skill in the art would have had a reasonable expectation of success of devising a method of delivering an oligonucleotide into a target cell comprising introducing the oligonucleotide into a target cell and contacting the target cell with the donor cell under conditions permitting the donor cell to form a gap junction channel with the target cell, whereby the oligonucleotide is delivered into the target cell from the donor cell since Frendo et al., Li et al. and Burt et al. taught the successful use and design of such a method at the time of invention. One of ordinary skill in that art would have had a reasonable expectation of success of substituting the antisense oligonucleotide composed of DNA taught by either Frendo et al., Li et al. and Burt et al. with a siRNA since the substitution of one known element for another would have yielded predictable results at the time of the invention.

Therefore, the invention would have been *prima facie* obvious to one of ordinary

skill in the art at the time of filing.

### ***Conclusion***

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James "Doug" Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer

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your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

September 11, 2008

/Terra Cotta Gibbs/